Identifying the Vulnerable Plaque

Moderator: Jim Zidar
Panel Members: Klemens Barth, Mike Cowley, Jim Zidar

Jim Zidar: We have chosen magnetic resonance imaging as our primary imaging tool at Duke University. A new cardiac magnetic resonance imaging research laboratory is being installed at Duke, with an adjacent clinical laboratory. In our view, magnetic resonance imaging will be an effective tool as it evolves, but there are many unanswered questions at present. The IAGS may be the ideal society to launch collaborative research on a unique topic. I don’t think we have found the optimal technology yet. I talked to Tom Linnemeier about this on several occasions. Tom has received proposals from several smaller companies who are trying to identify vulnerable plaque both through invasive and noninvasive methods.

Mike Cowley: There are several approaches that can be employed to evaluate this. One approach involves identifying not only the culprit lesion in the patient who comes to the cath lab for a clinical reason, but the other sites that are at risk for future events as well. While that patient is in the cath lab, invasive techniques such as thermography, MR probes — which are very effective — or even some of the IVUS techniques can be performed. The other approach involves identifying culprit lesions with biological markers in patients who are potentially at high risk. It would be ideal to have a biological marker that predicts the activity — like thermography predicts activity, invasively. Most of the markers now available indicate that an event has occurred and they remain elevated for several months, but they are not precise enough to identify potential problems. Techniques such as EBCT or markers such as C-reactive protein can help identify those patients for whom more invasive evaluation is required. For the broader population base, we must find a non-invasive screening technique that can identify patients who are at risk. Statin drugs have proved to be very potent and effective at changing the inflammatory profile, which has correlated with decreases in event rates. The slide Kirk Garratt just showed indicated that there were very miniscule changes in lumen diameter and that there were marked decreases in events. This essentially means that the composition, rather than the severity, of the plaque is being altered. Some of the magnetic resonance images — whole body, non-invasive tests — can now highlight very small, third order, and branch vessels. Perhaps if some of these techniques were paired, we would be able to identify the warmer plaques. There is certainly a lot of interesting research under way in this area, but we still don’t know enough about the biology of vulnerable plaque to develop effective screening techniques.

Klemens Barth: From a practical standpoint, we should look at computed tomography because, as you know, CT is now available with four slices per revolution and will achieve sixteen slices per revolution this year. Computed tomography is a very fast imaging technique that has already demonstrated its potential. Research was conducted last year at the University of Tübingen which identified plaque by Hounsfield units. This study showed that the plaque that has Hounsfield units between -6 and +50 has a high lipid content. Calcified plaque with Hounsfield units in the 100s range is probably the more stable plaque. Multi-slice computed tomography is a non-invasive imaging technology that could potentially identify unstable plaque. Also, from an availability and practical standpoint, computed tomography is the most likely technique to provide the answers.

Kirk Garratt: Do you think that the EBCT technique is really likely to play out very well? My understanding of the literature, which is admittedly incomplete, leads me to conclude that EBCT is very good at identifying the presence of advanced atherosclerosis. EBCT seems most effective in identifying the mature fibrocalcific plaques that present low risk of rupture, which probably explains the relatively poor correlation between EBCT scores and adverse clinical events in the short-term.

Klemens Barth: I think that is true. EBCT is basically on its way out; its use is not on the rise. Multi-slice computed tomography will take over completely. And if it’s true that multi-slice CT can identify a lipid-laden plaque by Hounsfield units, then it will be a very useful tool.

Kirk Garratt: Can that in fact be done? Can a multi-slice helical CT be tuned to provide information about lipid burden just like with calcium burden?

Klemens Barth: Yes. Multislice helical CT can identify small differences in tissue density. The limitation may lie in the spatial resolution.

Gary Roubin: How many people in this room are now taking statins? Most of the patients we see and most physicians I know are already taking some dose of a statin drug. We know that even if one has normal cholesterol, statins confer longevity in terms of cardiovascular events. The next step beyond this baseline therapy is to identify plaque that is still vulnerable. There is a market potential here for the imaging and the interventional device companies and we must increasingly look to them, not the pharmaceutical companies, for research funding. If we could identify those patients with vulnerable plaque in the carotid bifurcation as a window to what’s going on in the rest of their arterial system, we could then use that information to modulate in some way what is going on in the entire cardiovascular system with more aggressive pharmacologic or mechanical approaches to reduce the lipid load in that plaque. Alternatively, those patients could be brought to the cath lab or the interventional suite where we would look for vulnerable plaque in critical areas such as the carotids and the coronary arteries. Then, we could use some of the other technology you mentioned to identify plaques and treat them with drug-coated stents.

Kirk Garratt: Gary, back in the 1980s, you conducted a rather unconventional study at Emory University in which you tested what happened when non-critical 50% stenosed lesions...
were dilated early on. Your study showed that this method changed a relatively quiescent atheroma into a more aggressive restenosis. Let’s say now that coated stents are available and, for the sake of argument, they are inexpensive — which is a bold assumption, but there’s no harm in fantasizing! What would you think about imitating the Gary Roubin-style research of the early 1980s by taking a population of patients and pre-emptively striking the proximal LAD, the proximal circumflex, and the proximal right coronary artery? The pre-emptive strike would change the natural history of the lesions — not in a six-month time frame, but in a twenty-year time frame — by placing a device such as a coated stent in the coronary arteries. What is your opinion on that?

**Gary Roubin:** Back then, we applied fairly crude balloon angioplasty and soon realized that we could induce in mild to moderate lesions more disease than we were curing by ballooning those lesions. This was done before the animal work had been conducted. Later, after the animal studies were completed, we realized that we could have predicted this outcome because of Gruenzig’s cautious step-by-step approach. We didn’t do any harm to the patients, however. The same studies must be conducted prospectively in very rigorous trials with drug-coated stents. It may be that drug-coated stents are not the answer; cryotherapy may be the answer — who knows? Perhaps some sort of heat therapy could be revamped to treat these vulnerable plaques, or it may simply be a question of applying a pharmacological intervention to the plaque to toughen it up. A number of potential therapies exist to treat vulnerable plaques, but obviously, each one must undergo rigorous testing.

**Mike Walker:** Coronary arteries, because of their encasement, are difficult to get at. There has been a lot of ultrasound work done in the periphery, particularly in the carotid arteries, by people such as Andrew Nicolades and a number of Europeans, looking at plaque and grayscale in relation to event rates. There is also an increasing amount of research being conducted in the area of genetic and serum markers as a means to further risk stratify patient groups. This research is definitely in the preliminary stages, but it will likely be useful in the future.

**Richard Myler:** As some of you may know, I have written a great deal about what I call the unstable plaque, to differentiate it from the vulnerable plaque. Vulnerable implies that it’s before the fact and that it might become unstable. Once a plaque is unstable, however, it means that something has happened — at least to my understanding. I would like to give credit here not only to Val Fuster, but also to Michael Davies, whom I have never met, and to Erlene Falk, with whom I have had many discussions on this topic. Not all vulnerable plaques become unstable, and we don’t know yet what to do about this. Some of the simpler approaches involve “toughening up” the plaque, decreasing cholesterol levels, and thickening the fibrous cap. We have not yet mentioned here that when the plaque cracks or fissures, a series of events occur. I have tried to contemplate why these events occur, and the key, of course, is the platelet. When a crack occurs, approximately 50,000 platelets migrate to its surface within seconds. Perhaps the platelet is programmed to seal arterial lacerations, and perhaps the platelet sees this crack as a mini laceration. In a way, it is a laceration. Thus, perhaps we can use the platelet as a marker of instability, as a carrier of something to stabilize that plaque. I think it is one of the most fascinating pathologic and clinical pathologic conditions we deal with — and we deal with it frequently and, invariably, in acute situations.

Like the group at Emory University, we conducted some early studies in the area of angioplasty on unstable angina patients. This approach could be compared to flying a balloon into Afghanistan during the war. It was not the place to fly a balloon; it was dangerous and could cause trouble. We found this to be true with angioplasty on unstable angina patients because the procedure merely added insult to injury by provoking increased platelet aggregation — an undesirable event in the acute setting.

**Kirk Garratt:** I think you are exactly right. Our current challenge is to think about these unstable plaques preemptively and identify which will be the vulnerable plaques that settle down and which will not. I like what you said about platelets, Richard. My personal opinion, however, is that we need to pay more attention now to white cells. We already understand a good deal about platelets and have some fairly effective drugs to modify their behavior, but there is not much currently available to modify white cell behavior. It does seem that the white cell, particularly macrophages and mononuclear cell species, really is the key player in this process.

**Richard Myler:** It is not just the platelet; it’s what’s inside the platelet and the release of those active compounds that causes this enormous instability for whatever reason.

**Michael Lawrence Brown:** Kirk, in your images, I did not see much on hemorrhage in the plaque. In the area of carotid disease, we go back to the carotid bifurcation as a possible window into understanding this. We know there is a difference in the behavior of those patients who are symptomatic versus those who are asymptomatic, and the plaque seems to be different. When I perform an endarterectomy on a symptomatic patient, I expect there to be hemorrhage within the wall. We look at the plaque and think of it as degenerated, and then it ruptures. The idea is that the intima gives way. We also know that hematomas in an artery wall can be caused by trauma and will heal. We also know that hematomas will break down to form cholesterol. What about the idea that a microfracture occurs due to a fatigue fracture within the artery wall, which is followed by healing? And at some stage, it may be that the integrity of the media or the subintimal area is genetically weaker in some people who are susceptible to hemorrhage. The problem is thus being considered in reverse. I can understand why a person dies in his sleep when his circulation is reduced to the lowest level and there is a tight stenosis causing thrombosis. It may be related to a stasis and to platelet aggregation on a rough surface. However, I really do not understand why a man who is in the middle of prime years and is working as hard as he can to save his life in a storm, suddenly dies of a heart attack. I don’t believe it is due to an arrhythmia.

In this instance, I think that the artery fractures because it is at that time that the man’s blood pressure is highest, his pulse rate is the fastest, and the stress on his artery is the greatest.
has existed for years is weakened in that plaque, rendering it vulnerable in that fracture event. I don’t know whether it’s actually a fracture of the fibrous cap or just some gradual erosion or bursting from beneath, but what you say is true: It is the patient who fracture of the fibrous cap or just some gradual erosion or burst-

Kirk Garratt: Let me make sure I understand. You argue that it is perhaps the natural stress which takes place across the diseased vessel wall that causes disruption. That disruption process and the subsequent healing are what contribute to the inflammation and the lipid pool which can be secondary to an initial fracturing event and secondary healing. We tend, however, to think of it the other way around in that there is something driving that disease process initially which results in a secondary fracture. Am I reflecting your thoughts accurately?

Michael Lawrence Brown: Yes. What happens is that the initial event is an injury to the artery wall caused by the stresses and strains it undergoes. It then heals and forever becomes a vulnerable point, becoming cyclical until there is a symptomatic lesion in the carotid or a vulnerable plaque in the artery.

Kirk Garratt: If this is correct, then perhaps in addition to statins and aspirin, everyone should also be taking beta-blockers.

Michael Lawrence Brown: The HOPE trial using Ramipril showed that fewer cardiac events will occur if blood pressure is controlled.

Richard Myler: The platelets invade the plaque; I want to make that clear. Once a crack occurs, the platelets come inside the plaque and try to seal it. With that invasion and the release of many platelet activating factors, a clot may form to seal the initial crack. Unfortunately, the vasospasm caused by the release of the active factors and the clot formation may result in occlusion of the vessel. Teleologically, one can understand that if the platelet sees this as a laceration in the artery, it will seek to stop the flow in that artery and therefore to stop the hemorrhage, which can kill the organism. It is thus very complicated. It took a long time to get over the idea that this crack in the plaque directly released material into the atheroma. That may occur, but it is not the pathophysiology of what has been discussed here today. I think that platelets may be key for some of the diagnostic studies and are certainly key in terms of affecting therapy.

Peter Gonschior: We studied 35 autopsy vessels and found a lot of immuno-histo chemistry and histologic staining. But the most significant finding was that cracked plaque was averted in elastic fibers. There are 16 to 17 different elastic fibers. The most significant finding was an enhancement of collagen-1 deposition in these cracked plaques which led to death in 85% of these patients.

Kirk Garratt: That is interesting. What do you make of that? It is certainly a provocative observation.

Peter Gonschior: I think that the elastic potential of the vascular wall is altered and the balance of elastic fibers and stiff fibers changes. I don’t know why this occurs. Other than diabetes, no other predictive factors were found.

Kirk Garratt: Did I understand correctly that there was an increase in the content of elastic fibers?

Peter Gonschior: Yes, there was an increase of stiff collagen-1 fibers. Collagens-3 and -6 are very elastic fibers, whereas collagen-1 is a very stiff and large fiber.

Raoul Bonan: I would like to return to what Gary Roubin was saying about going back to an animal model. If we can find an animal model to show how to change a vulnerable plaque back into a pacified plaque, it will enhance the diagnosis of these patients. If there is no specific therapy to offer, we will use IVUS as a diagnostic tool. We must put effort into studying an animal model such as the rabbit to help us explain or reverse it.

Kirk Garratt: There was a question earlier about plaque rupture and hemorrhage, which reminds me to say that we should keep in mind the fact that not all patients who experience these acute clinical syndromes have the same underlying pathobiology; it is the ruptured plaque that accounts for most of them. I will now show you two additional slides. This first slide is of a very young woman who had a witnessed cardiac arrest and died. She had thrombosed a coronary artery. What was seen on the pathology study was that, in fact, the underlying atheroma was a predictably quiescent fibrotic one. Coronary disease was present, but it did not look like the active, lipid-laden disease that would normally be associated with these kinds of clinical events. On the surface of her atheroma, however, there were a lot of inflammatory cells and some erosion on the surface with superimposed clot. Something was driving an inflammatory process on the surface of this plaque that still defies explanation. Renu Virmani claims that approximately 15% of pathologic specimens of myocardial death will show this sort of pathology — not the classic ruptured plaque event. This slide shows the intramural hematoma which is the other form of acute coronary syndrome where the plaque rupture does not lead to luminal thrombosis, but rather causes sudden bleeding into the vessel wall. This bleeding leads to an acute compressive effect on the coronary circulation and, presumably, on the cerebral circulation as well, which can cause sudden adverse events. This next slide shows a more rare event, but it can happen. This dramatic photograph of an unstable plaque never fails to impress me. The rupture did not occur at the shoulder zones with this particular plaque, rather, it happened right in the center of the plaque. This relatively large cholesterol pool was spilled into the lumen in a volcano-like eruption of that plaque, with a sudden showering of all these cholesterol crystals into the coronary microvasculature, which was documented pathologically as well. That patient died so suddenly that he virtually had no time to develop superimposed thrombosis. Vulnerable plaque is thus at the root of much of this disease, but not all of it. There are many ways we can die from this stuff.

Nick Hopkins: The preliminary reports on intracranial angioplasty and stenting showed very high morbidity and mortality rates
associated with the procedure — particularly in symptomatic patients. As Dr. Myler suggested, it is risky to treat an unstable plaque. Others have reported that if suboptimal angioplasty is performed in these really sick intracranial plaque patients who are symptomatic, the vessel can be opened slightly to improve flow with very low risk if the proper antiplatelet regimen is maintained.

We performed suboptimal angioplasty in eight symptomatic patients who had some really ugly, long, eccentric lesions. We opened their vessels just slightly, pushing the plaque out against the wall. We waited a couple of months after the angioplasty procedure before placing a stent in these patients, thinking that perhaps we had injured that plaque and then created a moderate healing response that would render it more stable. Does that make any sense?

**Kirk Garratt:** Yes, it does. Many of us have had similar feelings about acute infarct intervention. The most dreaded complication of an otherwise successful intervention would be the no-reflow phenomenon that develops when we shower debris distally, which does not usually happen with the initial balloon dilatation. Rather, it tends to happen when the stent is placed after the vessel is opened. My view, which is probably a widely held one, is that in these cases, we are shredding that friable, vulnerable plaque and its overlying thrombosis with the stent and are allowing that debris to take off. Perhaps we should do exactly what you described, Nick; that is, open the vessel, let the area heal and firm up, and then stent it.

**Nick Hopkins:** We observed no major complications in that tiny patient subset; no major neurologic morbidity.

**Jim Zidar:** It also may be that the intracranial vessels are more fragile. We used to try to go easy and just get the vessel open. Perhaps the coronary arteries are a tougher anatomy and the heart can handle it better. Many practitioners push forward with aggressive antiplatelet therapy and try to achieve a good outcome.

**Nick Hopkins:** Yes, that is part of the rationale. We know that if you take acute intracranial pathology and treat it the way you would normally treat the coronary arteries, that is, achieve a pristine angiographic result, there will be a high incidence of rupture. The intracranial vessels are much more fragile.

**Jim Zidar:** There must be a difference in the vessel wall morphology.

**Nick Hopkins:** Yes, the intracranial vessels are much thinner.

**Kirk Garratt:** Do they dissect, Nick? Or are there just embolic events?

**Nick Hopkins:** Dissection and rupture occur.

**Raoul Bonan:** I think there is smooth muscle cell proliferation. The vessel is opened slightly, just to pass through, but the injury caused by the passage stimulates smooth muscle cell proliferation. The crust needs to be thicker and that kind of fibrosis is needed to seal and pacify the vulnerable plaque. That is probably what is occurring.

**Nick Hopkins:** We hope that’s what we are doing.

**Jeff Werner:** The slide you showed a moment ago on the 33-year-old woman is very interesting for several reasons. An autopsy study published in the last couple of years in Circulation involved women under 55 years of age who died a sudden death on the streets of New York city. All of them had autopsies. The vast majority of these women showed exactly what you did on that slide: they had relatively non-occlusive atherosclerosis and had ruptured plaque with acute thrombosis or had intramural hemorrhage that caused closure. I have read many explanations for why women don’t have symptoms. Some women do, but we cardiologists apparently don’t listen to them or their symptoms are atypical. I believe that it is probably more likely that these women don’t have symptoms because there is something that causes this to be more common in women than in men. These patients with no symptoms represent another reason why we must identify unstable plaque early on.

**Kirk Garratt:** Yes. Understanding the spectrum of the underlying pathology becomes key if we are talking about a medical cure, because I don’t think statins would have helped that 33-year-old patient. Perhaps anti-inflammatory and antiplatelet agents would have helped her, but they would not have helped the male patient who had sudden cholesterol emboli that killed him quickly. Thus, it is a very difficult mix.

**Douglas Cavaye:** In Los Angeles, we tried to make plaques in dogs in the early 1990s when IVUS was new. One of the most effective methods was to use a balloon that was slightly larger than the artery. Interestingly, we had much greater success making a plaque at the bifurcation of the canine aorta than in the common iliac artery, which raises the question of whether the bifurcation itself is susceptible to mechanical stress compared to the straight vessel. We also tried to make lesions in canine external iliac arteries just proximal to the groin. When imaged with IVUS, if we went to flat, approximately 90% of them healed — no stenosis. Thus, using an angioscope, we had to subintimally inject some of the dogs’ own blood. More than 75% of the time, a good stenosis was achieved at six weeks. Admittedly, this was not plaque, but it adds weight to the argument that Michael Lawrence Brown made regarding the initiating event as perhaps being related to the site: high-shear stress, low-shear stress movement, as well as the subintimal hematoma, rather than just external elastic stretch leading to rupture.

**Richard Myler:** Many of us have patients on whom we have successfully performed angioplasty and have followed them up for decades. Obviously, we have seen these patients develop atherosclerosis over that period of time. However, I cannot recall a single patient in that follow-up period who developed a new lesion on an old plaque that had been successfully treated. New lesions may form near an old one, or in other vessels, but it raises the question about taking what might have been an unstable or somewhat vulnerable plaque and healing it somehow so that a thicker fibrous cap forms and protects the plaque from future mischief.

**Kirk Garratt:** That is a good point, Richard. It is quite a mystery in my mind, because I don’t understand why scaling over one plaque zone changes the history of atherosclerosis in that zone so dramatically. It presumably neo-endothelializes. Isn’t that a new endothelial layer that should be prone to the same systemic disease and recruit the same white cell infiltration? The vessel itself does not remain scarred on the surface. We can stop antiplatelet drugs after a period of time because the scar neo-endothelializes. I don’t understand why atheroma does not develop on top of the scar.

**Paul Overlie:** I would like to hear from the panel members.
about risk stratification. We spend so much time risk stratifying patients who have acute infarcts. Are we approaching an era — and how close are we to it clinically — where we will be able to risk-stratify the lesions we observe in terms of those that need attention soon and those that can be watched? Many of us see lesions that are 50% stenosed and are embarrassed two weeks later when those patients return with an acute infarct in that exact location.

Jim Zidar: At Duke, our new chief, Pascal Goldsman, is very interested in genomics, genomic markers, and platelets. A large variety of platelet receptors exists in the population. For the past year and a half, patients who come to our cath lab sign a consent form to give 35 ccs of blood. Dr. Goldsman’s goal is to acquire between 5,000–10,000 samples. He is studying these blood samples and correlating them with prior angiograms to determine which patients have subsequent events in the ensuing five years relative to various markers — whether inflammatory or platelet receptor markers — and then looking back at their pathology as a way to expand the database which has historically been comprised of normal risk factors. The ordinal scale ranges from 25%, 50%, 75%, 95% and 100% stenoses. This long-term study will thus examine genetic marker data in comparison to patient anatomy and clinical outcomes. I can’t think of any other way to get to the bottom of this question.

Gary Roubin: Although I admit that Dr. Goldsman is doing excellent work, the problem I see is that there are so many steps and so many genes involved with respect to the plaque: first it’s vulnerable, then unstable, then a clinical event occurs. I think it will be a very long time before we get to the bottom of the question. But, I agree, we need to start somewhere.

Mike Cowley: It may be possible to identify the patient at risk, but it is impossible at this point to determine which of the little 30%–40% stenosed plaques located in other arteries present a risk to that patient.

Gary Roubin: This is another example of molecular research that has been consuming vast amounts of financial resources over the past decade without providing truly useful information to those of us in the field. A lot of money has been wasted on basic research that really has led us nowhere. In my view, the rooster and rabbit models of lipid-laden plaques merit closer study. I have recently observed some truly remarkable technology tested in a rooster model that can remove lipid from plaques. In my twenty years of involvement in atherosclerosis research, I have never seen anything like this. It also removed all the fat from the abdominal cavity of the rooster as well, which has other social implications, I’m sure! (laughter)

I do want to take Nick to task a moment here. Having worked in both the brain and the heart for over a decade now, I have clearly observed that the vessels in the brain are fundamentally different from those of the heart. The brain, as an organ, is far less vulnerable than the neuroradiologists, the neurosurgeons, and the vascular surgeons would have interventional cardiologists believe. The brain has an incredible ability to withstand large quantities of embolic debris and insults. Otherwise, how could you or the vascular surgeons ever have been successful? Every interventional cardiologist in this room has taken a patient for an elective procedure and had to walk out and tell the patient’s wife that her husband died on the table. There is nothing worse than having to deliver that news. It is much easier to warn every patient who goes in for elective cerebrovascular procedures that they have a 2% risk of stroke. We can at least lean on those words of warning when we have to tell the family that the patient had a stroke. That, in my opinion, is infinitely easier than what we face in interventional cardiology when a death occurs on the table. The heart is a much more difficult organ to treat than the brain, in my experience. However, we have been scared off from performing cerebrovascular interventions by people who have a vested interest in keeping this domain to themselves. I have worked in both disciplines now for over a decade, and I am much happier to work on the brain than on the heart.

Kirk Garratt: Nick, you look like you have a ready response to Gary’s comments. The gun is loaded and drawn! (laughter)

Paul Overlie: I want to return briefly to the subject of patients whom angiography shows a 50% lesion stenosis. I have some of these patients undergo a stress thallium test to see if that area hypoperfuses with stress. Are these new tools — the MRA, the multislice CT scan — going to be able to give us any more information about patients in whom we should intervene, despite the fact that their anatomy does not show very tight lesions?

Kirk Garratt: That is a very important, but perhaps different topic, because you are asking about the clinical relevance of an angiographically indeterminate lesion. I have access to tools in my cath lab that can help me sort that out. I will perform an FFR or a Doppler flow assessment which will provide the same information as a nuclear perfusion study. I am personally satisfied with that technology. What I am curious about now is the patient whose lesion passes the FFR test and then, one or two months later, suffers a big anterior MI.